Chapter 5

Analysis of tumor cells in the absence and presence of chemotherapeutic treatment: The case of Caputo-Fabrizio time fractional derivative

5.1 Introduction

The human body is constructed from cells. It produces cells and also destroys them. This process happens in a systematic way. But when this process of division of cells occurs in an uncontrolled way it becomes a disease called cancer. Tumor is also a kind of cancer where this uncontrolled growth occurs in solid tissues such as an organ, muscle, or bone [100, 101, 102]. Due to this property of cancer it is called a neoplastic

disease. These damaged cells replace the healthy cells as time increases and it spreads with time. At present time, many types of treatment and cure are in trend. In medical science, researchers and scientists are trying to find a permanent cure of this disease. Currently, therapies like targeted therapy, hormonal therapy, chemotherapy, radiation therapy and palliative care are available. Solid type of cancer is cured by the surgery. These therapies leave some bad effect and reactions on human body but that can be ignored. Chemotherapy is popular nowadays. In this treatment, cancer cells are destroyed by the diffusion process of medicine into affected cells. For different types of cancers different drugs or medicines are used and sometimes combination of two or more also used for diffusion into cells. Generally, drugs are categorized the drugs into two categories. The first type is cytotoxic which prevents the division process of cells. The second type is cytostatic which kills the cancer cells [103]. The drugs which are used for treatment are alkylating and anti-metabolites. The response of tumor cells for different types of drugs are different. When the drug ia injected into the part of the body where tumor is spreading, it diffuses to the tumor through the capillary surrounded by tumor cells. The interaction process between the immune cells and tumor cells is a very complicated process. Mathematical modeling and prediction is a useful tool to understand the complex biological behavior of physical problems [104, 105]. In the last few years, many mathematical models have been developed and modified on the basis of experimental data to explain the realistic behavior of such physical phenomena. One can find many mathematical models in the literature [106, 107, 108, 109]. By using fractional calculus the fractional version of such mathematical models are developed. Many researchers have considered the fractional model of tumor cells [110, 111, 112] to study the effect of chemotherapeutic treatment on cancer cells. Our immune system plays a crucial role in defending human body from the cancerous cells and also limits the development of these cells. There are two types of immune cells:(a) CD4 helper

tumor cells, which help other cells of the immune system to fight against cancerous cells [113];(b)CD8 killer cells, which directly destroy the tumor cells. Although having these effective immune cells, human body is unable to protect us from those cancerous cells due to the following reasons:

1. Our normal immune system is unable to identify cancerous cells from healthy cells. These cancerous cells are recognized as self and cannot be isolated as foreign cells. This phenomenon is known as tumor tolerance.

2. The immune system is able to recognize these cancerous cells, but immune cells are not strong enough to fight and give strong response against the tumor cells.

3. The ability and nature of tumor cells are the reasons that immune system cannot protect itself from tumor cells.

Thus the immune system must be boosted so that it can identify tumor cells and fight against them in an effective and efficient manner. There are many treatments available to deal with tumor cells such as chemotherapy, immune therapy, radiation-therapy and surgery. Each treatment is specifically applicable to different types of tumors based upon their locations and stages. The goal of these treatments is destruction or removal of tumor cells without damaging the healthy cells. Cytotoxic anti-neoplastic drug known as chemotherapeutic agent is used in the chemotherapy treatment. This treatment helps in destroying tumor cells and it also controls the dividation of tumor cells that divide rapidly in absence of treatment and therapy.
The present research contains the answers to the appropriate and relevant research questions on the dynamics of tumor model under different fractional order parameters, the behavior of tumor cells in absence or presence of chemotherapy treatment,

the distribution of tumor cells in spatial direction in tumor sites, and the effectiveness of immune system in destroying tumor cells.

The scientific report presented in article [110] derives the integer order model of tumor cells with chemotherapeutic treatment in the following way, which shows the effect of therapy on behavior of tumor cells. The aim of the chapter is to extend the model in fractional order system by replacing the integer order time derivative with the Caputo-Fabrizio time fractional derivative as

$$ {}_0^{CF}D_t^{\alpha}N(x,t) = D_N\frac{\partial^2 N}{\partial x^2} - a_3(1-e^{-U})N - c_4NT + r_2 \times N(1-b_2N), \tag{5.1}$$

$$ {}_0^{CF}D_t^{\beta}T(x,t) = D_t\frac{\partial^2 T}{\partial x^2} - a_2(1-e^{-U})T - c_3NT - c_2IT + r_1 \times T(1-b_1T), \tag{5.2}$$

$$ {}_0^{CF}D_t^{\gamma}I(x,t) = D_I\frac{\partial^2 I}{\partial x^2} - a_1(1-e^{-U})I - c_1IT - d_1I + \frac{\rho IT}{\mu+T} + \epsilon, \tag{5.3}$$

$$ {}_0^{CF}D_t^{\zeta}U(x,t) = D_U\frac{\partial^2 U}{\partial x^2} - d_2U + \vartheta(t), \quad 0 < \alpha,\beta,\gamma,\zeta \leq 1,\ 0 \leq t \leq 1. \tag{5.4}$$

Initially the integer order model was limited to chemotherapy treatment, but the other important medical treatments like immune therapy and radio therapy have not been considered. While in the later time and also in the aforementioned fractional order model those therapies have been taken care.

In section 5.2 of this chapter, an approximate formula for the C-F derivative of the function x^k and the operational matrix of C-F differentiation are derived. To solve this mathematical model, the operational matrix method is used in section 5.3. In section 5.4, the proposed method is incorporated. The numerical validation and study of the proposed model for different parameters are included in section 5.5. The last section 5.6 is devoted to the conclusion of overall work.

5.2 Derivation of C-F fractional differential operational matrix

5.2.1 Approximate expression of C-F derivative of simple polynomial function

The derivation of operational matrix of fractional integration and differentiation based upon Caputo and Riemann-Liouville can be found in [114]. In this section, the operational matrix of fractional order differentiation in C-F sense based upon shifted Chebyshev polynomial has been derived.

Theorem 7: The numerical approximation of C-F derivative of order $n < \nu < n+1$ of a function $f(\xi) = \xi^{\sigma}$ with $\sigma \geq \lceil \nu \rceil$ can be determined by

$$
{}_{0}^{CF}D_{x}^{\nu}\xi^{\sigma} = \frac{B(\nu)\Gamma(1+\sigma)}{\lceil \nu \rceil - \nu}\Big(\sum_{r=0}^{\sigma-n-1} \frac{(-1)^{r}\xi^{\sigma-n-1-r}}{\Gamma(\sigma-n-r)(\frac{-\nu}{\lceil \nu \rceil - \nu})^{r+1}} + \frac{(-1)^{\sigma-n}}{(\frac{-\nu}{\lceil \nu \rceil - \nu})^{\sigma-n}} \exp\big(\frac{-\nu}{\lceil \nu \rceil - \nu}\xi\big)\Big). \tag{5.5}
$$

Proof: As per the definition of C-F derivative, $D^{\nu}\xi^{\sigma} = 0$ for $\sigma = 0, 1, \cdots, \lceil \nu \rceil - 1$. For $\sigma \geq \lceil \nu \rceil$, the following expression is obtained.

$$
\begin{aligned}
{}_{0}^{CF}D_{x}^{\nu}\xi^{\sigma} &= \frac{B(\nu)}{\lceil \nu \rceil - \nu}\int_{0}^{\xi} D^{n+1}s^{\sigma}\exp\Big(\frac{-\nu}{\lceil \nu \rceil - \nu}(\xi - s)\Big)d\xi \\
&= \frac{B(\nu)}{\lceil \nu \rceil - \nu}\int_{0}^{\xi} \frac{\Gamma(\sigma+1)}{\Gamma(\sigma-n)}s^{\sigma-n-1}\exp\Big(\frac{-\nu}{\lceil \nu \rceil - \nu}(\xi - s)\Big)d\xi \\
&= \frac{B(\nu)}{\lceil \nu \rceil - \nu}\frac{\Gamma(\sigma+1)}{\Gamma(\sigma-n)}\exp\Big(\frac{-\nu}{\lceil \nu \rceil - \nu}\xi\Big)\int_{0}^{\xi} s^{\sigma-n-1}\exp\Big(\frac{\nu}{\lceil \nu \rceil - \nu}s\Big)d\xi
\end{aligned} \tag{5.6}
$$

$$= \frac{B(\nu)}{\lceil\nu\rceil-\nu}\frac{\Gamma(\sigma+1)}{\Gamma(\sigma-n)}\exp\Big(\frac{-\nu}{\lceil\nu\rceil-\nu}\xi\Big)\times$$
$$\Big[\exp\Big(\frac{\nu}{\lceil\nu\rceil-\nu}\xi\Big)\sum_{r=0}^{\sigma-n-1}(-1)^r\frac{\Gamma(\sigma-n)s^{\sigma-n-1-r}}{\Gamma(\sigma-n-r)(\frac{\nu}{1-\nu})^{r+1}}-\frac{(-1)^{\sigma-n-1}\Gamma(\sigma-n)}{(\frac{\nu}{1-\nu})^{\sigma-n}}\Big] \quad (5.7)$$

$$= \frac{B(\nu)\Gamma(\sigma+1)}{\lceil\nu\rceil-\nu}\Big[\sum_{r=0}^{\sigma-n-1}\frac{(-1)^r s^{\sigma-n-1-r}}{\Gamma(\sigma-n-r)(\frac{\nu}{1-\nu})^{r+1}}-\frac{(-1)^{\sigma-n-1}}{(\frac{\nu}{1-\nu})^{\sigma-n}}\exp\Big(\frac{-\nu}{\lceil\nu\rceil-\nu}\xi\Big)\Big]. \quad (5.8)$$

5.2.2 Chebyshev polynomials [16]

In this sub-section the Chebyshev polynomials and some of their properties are discussed. The Chebyshev polynomials are shifted from the interval $[0,1]$ to the interval $[-1,1]$ by the transformation $z = 2x-1$. The analytical form of these polynomials of degree i are given as follows:

$$\psi_i(x) = i\sum_{p=0}^{i}\frac{(-1)^{i-p}(i+p-1)!2^{2p}}{2p!(i-p)!}x^p, \quad (5.9)$$

where $i = 0, 1, \cdots$.

These polynomials are orthogonal in the interval $[-1,1]$ with respect to the weight function $\frac{1}{\sqrt{1-x^2}}$ and the orthogonality condition can be described as

$$\int_{-1}^{1}\frac{\psi_j(x)\psi_i(x)}{\sqrt{1-x^2}} = \begin{cases} 0, & j\neq i,\\ \pi, & i=j=0,\\ \frac{\pi}{2} & j=i\neq 0. \end{cases} \quad (5.10)$$

By shifting polynomials on the interval $[0,1]$, the weight function changes and now these polynomials are orthogonal on interval $[-1,1]$ with respect to the weight function $\frac{1}{\sqrt{x-x^2}}$.

A function $u(x)$ which belongs to the $L^2[0,1]$ can be approximated by a linear combination of shifted Chebyshev polynomials as

$$u(x) = u_m(x) = \sum_{j=0}^{m} a_j \psi_i(x), \tag{5.11}$$

where the linear coefficients are given by

$$a_j = \frac{c_j}{\pi} \int_0^1 \frac{u(x)\psi_i(x)}{\sqrt{x - x^2}}, \tag{5.12}$$

with $c_j = 1$ if $j = 0$ and $c_j = 2$ if $j = 1, 2, \cdots$. The equation (5.11) can be expressed in the matrix form as follows

$$u(x) = u_m(x) = \sum_{j=0}^{m} a_j \psi_i(x) = \mathbf{A}^T \Pi_m(x), \tag{5.13}$$

where

$$\begin{aligned} \mathbf{A}^T &= (a_0, a_1, \cdots, a_{m-1}), \\ \Pi_m(x) &= (\psi_0(x), \psi_1(x), \cdots, \psi_{m-1}(x))^T. \end{aligned} \tag{5.14}$$

In view of equation (5.11), the Chebyshev operational matrix of C-F derivative is derived which is presented in the following theorem.

Theorem 8: Let $\Pi_m(x)$ be the shifted Chebyshev vector with $n < \beta < n + 1$, then

$${}_0^{CF}D_x^{\beta} \Pi_m(x) = Q^{\beta} \Pi_m(x), \tag{5.15}$$

where Q^{β} denotes the $m \times m$ C-F operational matrix of order β. It can be defined as

$$Q^{\beta} = \begin{bmatrix} 0 & 0 & \cdots & 0 \\ 0 & 0 & \cdots & 0 \\ \vdots & \vdots & \cdots & \vdots \\ \sum_{p=\lceil\beta\rceil}^{\lceil\beta\rceil} \varsigma_{\lceil\beta\rceil,p,1} & \sum_{p=\lceil\beta\rceil}^{\lceil\beta\rceil} \varsigma_{\lceil\beta\rceil,0,p} & \cdots & \sum_{p=\lceil\beta\rceil}^{\lceil\beta\rceil} \varsigma_{\lceil\beta\rceil,m-1,p} \\ \vdots & \vdots & \cdots & \vdots \\ \sum_{p=\lceil\beta\rceil}^{i} \varsigma_{i,0,p} & \sum_{p=\lceil\beta\rceil}^{i} \varsigma_{i,1,p} & \cdots & \sum_{p=\lceil\beta\rceil}^{i} \varsigma_{i,m-1,p} \\ \vdots & \vdots & \cdots & \vdots \\ \sum_{p=\lceil\beta\rceil}^{m-1} \varsigma_{m-1,0,p} & \sum_{p=\lceil\beta\rceil}^{m-1} \varsigma_{m-1,1,p} & \cdots & \sum_{p=\lceil\beta\rceil}^{m-1} \varsigma_{m-1,m-1,p} \end{bmatrix},$$

where $\varsigma_{i,j,p}$ is obtained by the following relation

$$\varsigma_{i,j,p} = \frac{i(-1)^{i-p}(i+p-1)!2^{2p}}{2p!(i-p)!} \times \frac{B(\beta)\gamma(1+p)}{\lceil\beta\rceil-\beta}\Big[\Xi_1(p,j,x) + \Xi_2(p,j,x)\Big],$$

and

$$\Xi_1(p,j,x) = \frac{(-1)^{p-\lceil\beta\rceil}}{\gamma^{p-\lceil\beta\rceil}}\Big(\sum_{l=0}^{j} \frac{j(-1)^{j-l}2^{2l}(j+l-1)!c_j}{2l!(j-l)!\pi} \times \sum_{s=0}^{l} \frac{\sqrt{\pi}\Gamma(\frac{1}{2}+l)(-1)^s\gamma^{s-1}}{s!\Gamma(s+l+1)}(\frac{1}{2}+l)(\frac{3}{2}+l)\cdots(\frac{2r-1}{2}+l)\Big) \tag{5.16}$$

$$\Xi_2(p,j,x) = \sum_{r=0}^{p-\lceil\beta\rceil-1} \frac{(-1)^r}{\Gamma(p-n-r)\gamma^{r+1}}\Big(\sum_{l=0}^{j} \frac{j(-1)^{j-l}2^{2l}(j+l-1)!c_j}{2l!(j-l)!\pi} \times \frac{\sqrt{\pi}\Gamma(\frac{-1}{2}+p+l-n-r)}{\Gamma(p+l-n-r)}\Big). \tag{5.17}$$

Here $\gamma = \frac{\beta}{1-\beta}$ and the ranges of i and j vary for $i = \lceil\beta\rceil, \cdots, m-1$ and $j = 0, 1, \cdots, m-1$ respectively.

Proof: By using Theorem 7, the following expression is obtained

$$ {}_0^{CF}D_x^{\alpha}x^p = \frac{B(\alpha)\Gamma(1+p)}{\lceil\alpha\rceil-\alpha}\Big(\sum_{r=0}^{p-n-1}\frac{(-1)^r x^{p-n-1-r}}{\Gamma(p-n-r)\gamma^{r+1}} + \frac{(-1)^{p-n}}{\gamma^{p-n}}e^{-\gamma x}\Big). \tag{5.18} $$

The C-F derivative of the i-th degree shifted Chebyshev polynomial is

$$ {}_0^{CF}D_x^{\alpha}\psi_i(x) = i\sum_{p=0}^{i}\frac{(-1)^{i-p}(i+p-1)!2^{2p}}{2p!(i-p)!} \times {}_0^{CF}D_x^{\alpha}x^p, \quad i=0,1,\cdots \tag{5.19} $$

$$ = i\sum_{p=\lceil\beta\rceil}^{i}\frac{(-1)^{i-p}(i+p-1)!2^{2p}}{2p!(i-p)!} \times \frac{B(\alpha)\Gamma(1+p)}{\lceil\alpha\rceil-\alpha} \tag{5.20} $$

$$ \times \Big(\sum_{r=0}^{p-n-1}\frac{(-1)^r x^{p-n-1-r}}{\Gamma(p-n-r)\gamma^{r+1}} + \frac{(-1)^{p-n}}{\gamma^{p-n}}e^{-\gamma x}\Big). \tag{5.21} $$

The $(i,j)^{th}$ element $\rho_{i,j}$ of operational matrix Q^{α} is determined by taking inner product with shifted Chebyshev polynomial $\psi_j(x)$, $j=0,1,\cdots m-1$, as

$$ {}_0^{CF}D_x^{\alpha}\psi_i(x) = \sum_{j=0}^{m-1}\rho_{i,j}\psi_j(x) $$

$$ \rho_{i,j} = \langle {}_0^{CF}D_x^{\alpha}\psi_i(x), \psi_j(x)\rangle \tag{5.22} $$

$$ = i\sum_{p=\lceil\beta\rceil}^{i}\frac{(-1)^{i-p}(i+p-1)!2^{2p}}{2p!(i-p)!} \times \frac{B(\alpha)\Gamma(1+p)}{\lceil\alpha\rceil-\alpha} $$

$$ \times \Big(\sum_{r=0}^{p-n-1}\frac{(-1)^r}{\Gamma(p-n-r)\gamma^{r+1}}\langle x^{p-n-1-r}, \psi_j(x)\rangle + \frac{(-1)^{p-n}}{\gamma^{p-n}}\langle e^{-\gamma x}, \psi_j(x)\rangle\Big). \tag{5.23} $$

The above expression contains two inner products which are determined as follows. For the first one, the expression for inner product is derived as

$$\langle x^{p-n-1-r}, \psi_j(x)\rangle = \frac{c_j}{\pi}\int_0^1 \frac{x^{p-n-1-r}\psi_j(x)}{\sqrt{x-x^2}}dx \tag{5.24}$$

$$= \frac{c_j}{\pi}\int_0^1 \frac{x^{p-n-1-r}}{\sqrt{x-x^2}}\sum_{l=0}^{j}\frac{j(-1)^{j-l}(j+l-1)!2^{2l}}{2l!(j-l)!}x^l dx \tag{5.25}$$

$$= \frac{c_j}{\pi}\sum_{l=0}^{j}\frac{j(-1)^{j-l}(j+l-1)!2^{2l}}{2l!(j-l)!}\int_0^1 \frac{x^{p-n-1-r+l}}{\sqrt{x-x^2}}dx \tag{5.26}$$

$$= \frac{c_j}{\pi}\sum_{l=0}^{j}\frac{j(-1)^{j-l}(j+l-1)!2^{2l}}{2l!(j-l)!}\times\frac{\sqrt{\pi}\Gamma(\frac{-1}{2}+p+l-n-r)}{\Gamma(p+l-n-r)}. \tag{5.27}$$

For the second inner product

$$\langle e^{-\gamma x}, \psi_j(x)\rangle = \frac{c_j}{\pi}\int_0^1 \frac{e^{-\gamma x}\psi_j(x)}{\sqrt{x-x^2}}dx \tag{5.28}$$

$$= \frac{c_j}{\pi}\sum_{l=0}^{j}\frac{j(-1)^{j-l}(j+l-1)!2^{2l}}{2l!(j-l)!}\int_0^1 \frac{x^l e^{-\gamma x}}{\sqrt{x-x^2}}dx \tag{5.29}$$

$$= \frac{c_j}{\pi}\sum_{l=0}^{j}\frac{j(-1)^{j-l}(j+l-1)!2^{2l}}{2l!(j-l)!}\times\sum_{r=0}^{l}\frac{\sqrt{\pi}\Gamma(\frac{1}{2}+l)(-1)^r\gamma^{r+1}}{r!(l+r+1)!}$$
$$(\frac{1}{2}+l)(\frac{3}{2}+l)\cdots(\frac{2r-1}{2}+l). \tag{5.30}$$

Putting both inner products into equation (5.23), the value of $\rho_{i,j}$ can be obtained. Considering $\rho_{i,j} = \sum_{\lceil\beta\rceil}^{i}\varsigma_{i,j,p}$, the final desired result is obtained as

$$\varsigma_{i,j,p} = \frac{i(-1)^{i-p}(i+p-1)!2^{2k}}{2k!(i-p)!}\times\frac{B(\beta)\gamma(1+p)}{\lceil\beta\rceil-\beta}\Big[\Xi_1(p,j,x)+\Xi_2(p,j,x)\Big]. \tag{5.31}$$

The operational matrix obtained above is applicable to fractional order case. For the integer case the operational matrix is given by

$$\rho_{i,j} = \begin{cases} \frac{4i}{\eta_j}, & j = i - k, \\ 0, & otherwise, \end{cases} \tag{5.32}$$

where $k = 1, 3, \cdots m$ if m is odd and $k = 1, 3, \cdots m - 1$ if m is even. The function η_j is defined as

$$\eta_j = \begin{cases} 2, & j = 0, \\ 1, & j \geq 1. \end{cases} \tag{5.33}$$

5.3 Description of model representing the chemotherapy effect on behavior of tumor cells

In this present era, mathematical modeling is an important tool for understanding and analyzing the dynamical behavior and physical properties. In this section the model of tumor cells is discussed in the presence of chemotherapeutic effect. This model contains the four coupled PDEs defined through equations (5.1) – (5.2). This model has the parameters which represent the numbers of the normal cells N, tumor cells T and immune cells I. It represents the diffusion and reaction phenomena of tumor cells into normal cells. But the investigation of the time-fractional version of this model (5.1) – (5.2) is studied. This model contains many parameters with physical meaning which are described as follows:

(i) The parameters $r_1 \times T(1 - b_1 T)$ and $r_2 \times N(1 - b_2 N)$ in the right hand side of the equations (5.1) and (5.2) denote the logistic growth rate of tumor and normal cells respectively.

(ii) The parameters r and b represent the capita growth rate and carrying capacity respectively.

(iii) The kill rates of tumor, immune and normal cells are denoted by the parameters a_3, a_2 and a_1 respectively.

(iv) The parameters c_1, c_2, c_3 and c_4 correspond to the interactions among tumor, immune and normal cells.

(v) The external source rate of immune cells in equation (5.3) is denoted by ϵ. The external flux is considered to be constant.

(vi) The term $\frac{\rho IT}{\mu+T}$ corresponds to the defence mechanism of the body as it fights with the tumor cells.

(vii) The parameters d_1 and d_2 denote per capita death rate of I-cells and per capita diminishing rate respectively.

(viii) Here μ represents the immune threshold rate and ρ is the immune response rate.

(ix) The immune cells vanish naturally in a healthy human body having no cancer cells to prevent cell proliferation. The term c_1IT represents this fact and the short life time of immune cells.

(x) The agent that is used to kill the tumor cells also kills all other types of cells. The term $U(x,t)$ denotes the amount of drug at time t at the tumor site. For the fraction of cells killed, a saturation term $1-e^{-U}$ is added.

(xi) In equation (5.4), the external influx of the chemotherapeutic drug $\vartheta(t)$ is defined by

$$\vartheta(t) = \begin{cases} 1 & \varpi(j-1) \leq t \leq (j-1)\varpi + \tau, \\ 0 & otherwise, \end{cases}$$

TABLE 5.1: Description and approximate numerical values of parameters used in model (5.38 – 5.41).

parameters ↓	Explanation of parameters	Numerical values
a_1, a_2, a_3	Fraction of cells killed	$0.2, 0.3, 0.1$
b_1, b_2,	Carrying capacity	1, 0.81
c_1, c_2, c_3, c_4,	Competition term	$1, 0.55, 0.9, 1$
d_1, d_2,	Death rate	$0.2, 1$
r_1, r_2,	Per capita growth rate	$1.1, 1$
ϵ	Immune source rate	0.33
μ	Immune threshold rate	0.3
ρ	Immune response rate	0.2
D_N, D_T, D_I, D_U	Diffusion coefficients for normal, tumor, immune system cells and the chemotherapeutic drug	$0.001, 0.001, 0.001, 0.001$

Here, τ represents the time duration and ϖ time interval.

(xii) Diffusion coefficients for normal, tumor, immune and chemotherapeutic therapy are denoted by D_N, D_T, D_I and D_U respectively.

The choice of initial conditions for this tumor model is very important as growth of tumor cells or its eradication are functions of these conditions. The initial conditions which are taken by us are in accordance with biological observations. According to research findings human body defence mechanism sends immune cells in bulk. It is assumed that the concentration of normal cells is greater than the tumor cells. In the present study it also assumed that tumor is large enough so that it can be detectable by medical instruments. The number of initial normal cells is in the order of 10^{11}. By taking into account all these observations the following initial conditions

have been taken [103].

$$T(x,0) = h_2(x) = 1 - 0.75\,\mathrm{sech}\,x, \tag{5.34}$$

$$N(x,0) = h_1(x) = 0.2e^{-2x^2}, \tag{5.35}$$

$$U(x,0) = h_4(x) = \mathrm{sech}\,x. \tag{5.36}$$

$$I(x,0) = h_3(x) = 0.375 - 0.235\,\mathrm{sech}^2\,x, \tag{5.37}$$

Using the slope of linear regression through the data points used in references [115, 116, 117, 118], it is worthwhile to consider the following:

(i) The distributions of normal cells with x decrease at the rate of 4.50578×10^{-19}.

(ii) There exists no such changes in the distributions of tumor cells with x.

(iii) The distributions of immune cells with x decrease at higher rate of 9.01155×10^{-19}.

(iv) In the case of chemotherapeutic drug, $U(x,0)$ increases with x at the rate of 7.20924×10^{-18}.

5.4 Solution of the problem

In this section, after deriving a new shifted Chebyshev C-F operational matrix, the collocation method is applied to investigate the behavior of the following model (5.41) and to solve this model mathematically with the help of initial conditions (5.45).

Assuming $\lambda_1 = r_2 - a_3$, $\lambda_2 = r_1 - a_2$, $\lambda_3 = d_1 - a_1$, $\omega_1 = b_2 r_2$, and $\omega_2 = b_1 r_1$,

proposed model (5.1) − (5.4) reduces to

$$
\begin{aligned}
{}_0^{CF}D_t^{\alpha}N(x,t) &= D_N\frac{\partial^2 N}{\partial x^2} - a_3(1-e^{-U})N - c_4NT - \omega_1N^2 + \lambda_1N, && (5.38)\\
{}_0^{CF}D_t^{\beta}T(x,t) &= D_t\frac{\partial^2 T}{\partial x^2} - a_2(1-e^{-U})T - c_3NT - c_2IT - \omega_2T^2 + \lambda_2T, && (5.39)\\
{}_0^{CF}D_t^{\gamma}I(x,t) &= D_I\frac{\partial^2 I}{\partial x^2} + a_1(e^{-U})I - c_1IT - \lambda_1I + \frac{\rho IT}{\mu+T} + \epsilon, && (5.40)\\
{}_0^{CF}D_t^{\zeta}U(x,t) &= D_U\frac{\partial^2 U}{\partial x^2} - d_2U + \vartheta(t). && (5.41)
\end{aligned}
$$

Let us approximate the above unknown functions $N(t,x)$, $T(t,x)$, $I(t,x)$ and $U(t,x)$ as finite linear combinations of shifted Chebyshev polynomials as

$$
\begin{aligned}
N(t,x) &= \Phi^T(x).A.\Phi(t), && (5.42)\\
T(t,x) &= \Phi^T(x).B.\Phi(t), && (5.43)\\
I(t,x) &= \Phi^T(x).C.\Phi(t), && (5.44)\\
U(t,x) &= \Phi^T(x).D.\Phi(t). && (5.45)
\end{aligned}
$$

Here, A, B, C and D are unknown matrices of order $m\times m$ and $\Phi(t) = (\psi_1(t).....\psi_m(t))^T$ is a column vector whose elements are shifted Chebyshev polynomials. Now approximating the C-F fractional derivative of $N(x,t)$ with respect to time and with the help of Theorem 8, the following approximation is obtained

$$
{}_0^{CF}D_t^{\alpha}N(x,t) = Q^{\alpha}N(x,t) = \Phi^T(x).A.Q^{\alpha}\Phi(t), \tag{5.46}
$$

Similarly,

$$ {}_0^{CF}D_t^{\beta}T(x,t) = Q^{\beta}T(x,t) = \Phi^T(x).B.Q^{\beta}\Phi(t), \tag{5.47} $$

$$ {}_0^{CF}D_t^{\gamma}I(x,t) = Q^{\gamma}I(x,t) = \Phi^T(x).C.Q^{\gamma}\Phi(t), \tag{5.48} $$

$$ {}_0^{CF}D_t^{\zeta}U(x,t) = Q^{\zeta}U(x,t) = \Phi^T(x).D.Q^{\zeta}\Phi(t). \tag{5.49} $$

The approximations of unknown functions in terms of Chebyshev polynomials has been taken to approximate the initial conditions

$$ \Phi^T(x).A.\Phi(0) = h_1(x), \tag{5.50} $$

$$ \Phi^T(x).B.\Phi(0) = h_2(x), \tag{5.51} $$

$$ \Phi^T(x).C.\Phi(0) = h_3(x), \tag{5.52} $$

$$ \Phi^T(x).D.\Phi(0) = h_4(x). \tag{5.53} $$

Using the Chebyshev approximations of $N(t,x), T(t,x), I(t,x),\ U(t,x)$ and their Caputo-Fabrizio fractional derivatives in the given system of fractional order PDEs a residual system is obtained. This residual is collocated and given initial conditions at Chebyshev nodes. After this step a non-linear system of algebraic equations is obtained. This system is solved by using Mathematica 11.3 which helps to find the unknown matrices A, B, C and D.

5.5 Numerical simulation and results

In this section, first the validation of the proposed method is shown by using it in a particular form of the concerned model. The accuracy of the method is shown by obtaining the absolute error between exact and numerical solutions. After the

validation of the method, it is applied to solve the concerned fractional order model for different particular cases. It is shown how the tumor cells increase with time without chemotherapeutic treatment. The effects of fractional exponents on normal, tumor and immune cells are depicted graphically. During numerical computation the numerical values of the parameters considered are given in Table 5.1. The following particular case of proposed model is chosen to verify the validity and accuracy of the method

$$ {}_0^{CF}D_t^{0.9}N(x,t) = D_N\frac{\partial^2 N}{\partial x^2} - a_3(1-e^{-U})N - c_4NT - \omega_1 N^2 + \lambda_1 N + f_1(x,t), \tag{5.54}$$

$$ {}_0^{CF}D_t^{0.9}T(x,t) = D_t\frac{\partial^2 T}{\partial x^2} - a_2(1-e^{-U})T - c_3NT - c_2IT - \omega_2 T^2 + \lambda_2 T + f_2(x,t), \tag{5.55}$$

$$ {}_0^{CF}D_t^{0.9}I(x,t) = D_I\frac{\partial^2 I}{\partial x^2} + a_1(e^{-U})I - c_1IT - \lambda_1 I + \frac{\rho IT}{\mu+T} + \epsilon + f_3(x,t), \tag{5.56}$$

$$ {}_0^{CF}D_tU(x,t) = D_U\frac{\partial^2 U}{\partial x^2} - d_2U + \vartheta(t) + f_4(x,t). \tag{5.57}$$

Here $f_i(x,t), i = 1,2,3,4$ are chosen in such a way that the exact solutions of the above problem are

$$T(x,t) = 1 - 0.75 \times \exp(-t)\,\mathrm{sech}\,x, \tag{5.58}$$

$$N(x,t) = 0.2\exp(-t) \times e^{-2x^2}, \tag{5.59}$$

$$U(x,t) = \mathrm{sech}\,x \times \exp(-t), \tag{5.60}$$

$$I(x,t) = -0.235 \times \exp(-t)\,\mathrm{sech}^2\,x + 0.375. \tag{5.61}$$

The absolute error of the normal cell $N(x,t)$ is defined by $\Delta N(x,t) = |N_{exact(x,t)} - N_{approx(x,t)}|$, where N_{exact} and N_{approx} represent the exact solution and the approximate numerical solution obtained by using the proposed method, respectively. The

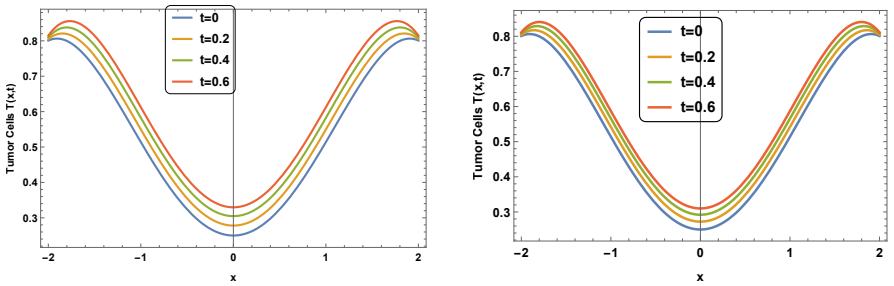
TABLE 5.2: Variations of absolute error for the unknown functions at fixed spatial point $x = 1$ for $m = 8$.

t ↓	$\Delta N(1,t)$	$\Delta T(1,t)$	$\Delta I(1,t)$	$\Delta U(1,t)$
0.2	3.4×10^{-3}	7.2×10^{-3}	3.4×10^{-4}	2.4×10^{-3}
0.4	6.4×10^{-4}	1.1×10^{-3}	6.7×10^{-5}	6.1×10^{-4}
0.6	4.3×10^{-4}	2.8×10^{-4}	5.5×10^{-5}	3.4×10^{-4}
0.8	1.3×10^{-4}	1.7×10^{-4}	2.8×10^{-5}	1.8×10^{-4}

absolute errors for other variables denoted by $\Delta T(x,t)$, $\Delta I(x,t)$, $\Delta U(x,t)$ are defined in a similar manner. For $m = 8$, the variations of the absolute errors are shown in Table 5.2 for different values of t at $x = 1$. It is clear from the table that proposed method is very efficient and has desirable accuracy.

5.5.1 Variation of tumor cells when chemotherapy drug is not injected

Chemotherapeutic drug can be injected into the patient's body by different methods. Some popular methods are intravenous injection, direct implantation, subcutaneous process in which the drug is directly implanted into the circulatory system and absorption is through the gastrointestinal tract. The aim is to show the behavior of tumor cells in the absence of chemotherapeutic drug. The results of this study are displayed through the graphs given in Fig.5.1. From the figure it is seen that the number of tumor cells increases with the increase in time in the absence of chemotherapeutic drug. As time increases from $t = 0$ to $t = 0.6$, the number of tumor cells increases. The number of tumor cells can be predicted with respect to the size of tumor site. The number of tumor cells increases at invasive fronts $x = -2$ and $x = +2$ when compared with the center of tumor $x = 0$. Fig.5.1(a) is plotted for integer case i.e., $\alpha = 1, \beta = 1, \gamma = 1, \zeta = 1$, while Fig 5.1$(b)$ is plotted for fractional orders $\alpha = 0.9, \beta = 0.9, \gamma = 0.9, \zeta = 0.9$. Here the graphs at time $t = 0, 0.2, 0.4, 0.6$



(a) Integer order case (b) Fractional order case

FIGURE 5.1: Growth of tumor cells at different time periods in absence of chemotherapeutic (a) for integer order system $(\alpha = 1, \beta = 1, \gamma = 1, \zeta = 1)$ (b) for C-F fractional order system $(\alpha = 0.9, \beta = 0.9, \gamma = 0.9, \zeta = 0.9)$.

are more closer compared to the integer order model given in Fig.5.1(a). Thus the growth of tumor cells as the time passes is less in case of C-F fractional model when compared to integer order model.

5.5.2 Behavior of tumor cells after applying chemotherapeutic treatment

In this subsection, the effect of chemotherapeutic drug on the number of tumor cells is studied. It is assumed that the therapy is applied per week and the interval for each dose is $\tau = 6$ hours. The external influx of agents in this therapy is assumed to be $\varpi = 7$ days. After injecting the drug into the tumor site, it started to kill the tumor cells. The graph of the tumor cells shows that the growth of tumor cells is slower in the presence of chemotherapeutic drug. From Figs. 5.1 and 5.2, it is observed that in the presence of drug $U(x, t)$ the increment of tumor cells is slower.

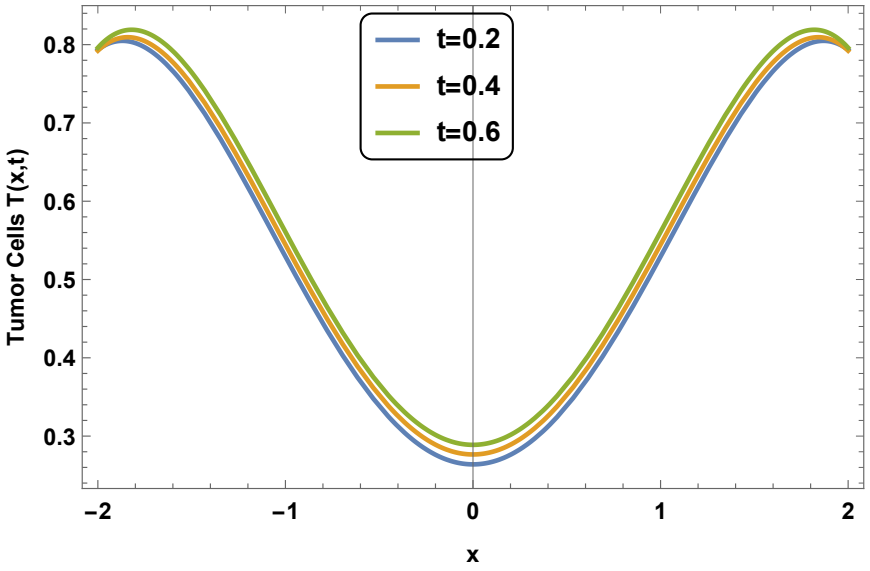


FIGURE 5.2: Graphical representation of tumor cells in presence of chemotherapeutic drug with different time intervals.

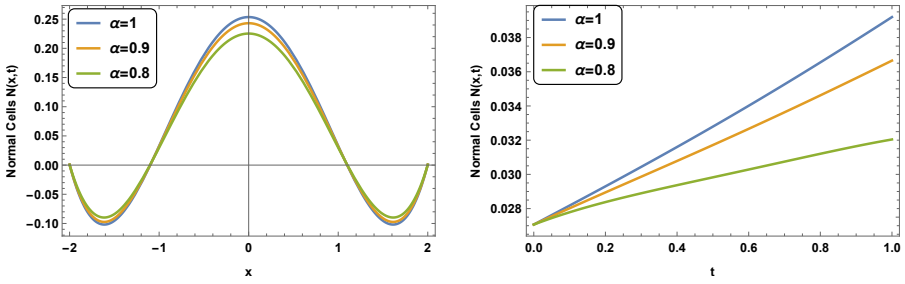
5.5.3 Discussion of the nature of model in fractional order system and future scope

In this subsection, the changing behavior of the model is found with change in its fractional order through the graphical representations Figs.5.3−5.6. This helps us to investigate the biological behavior of immune, tumor, normal cells and chemotherapeutic drug. The Brownian motion of normal cells is depicted through Fig.5.3.

The behavior of normal cells for different values of α in x and t directions is shown through Fig.5.3(a) and Fig.5.3(b) respectively. It can be observed that the concentration of normal cells increases in both directions as α increases from $\alpha = 0.8$ to $\alpha = 1$. From Fig.5.4(a), It is concluded that as β approaches from $\beta = 0.8$ to $\beta = 1$, the number of tumor cells increases.

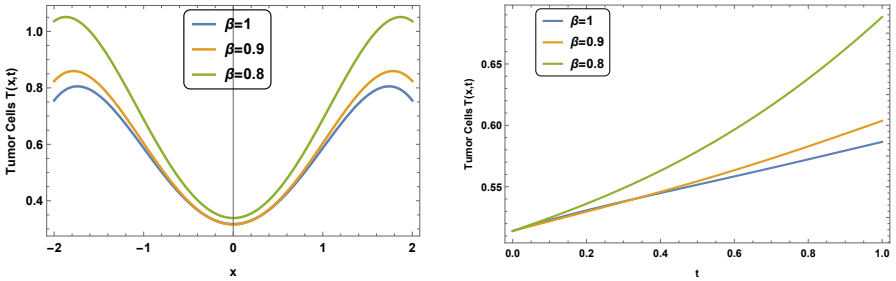
It is also seen from this figure that number of tumor cells is more at the boundary of tumor site (x approaches from 0 to 2 or -2). Fig.5.4(b) shows the behavior of tumor cells with respect to time. The number of tumor cells increases with time.

Fig.5.5 represents the behavior of immune cells for different value of γ along x and t direction respectively. It is observed that number of immune cells increases at invasive fronts of tumor site compared to the center and also increases with time from $t = 0$ to $t = 1$. Fig.5.6(a) shows that higher concentration of chemotherapeutic drug is needed at the center of tumor site compared to the outside walls of the site. Fig.5.6(b) depicts that at starting time $t = 0$ more concentration of drug is required since as time passes the concentration of drug decreases. In the context of future scope, the newly derived operational matrix can be applied to solve two or more dimensional FPDEs having C-F derivatives. This model can be studied with non-local derivatives.



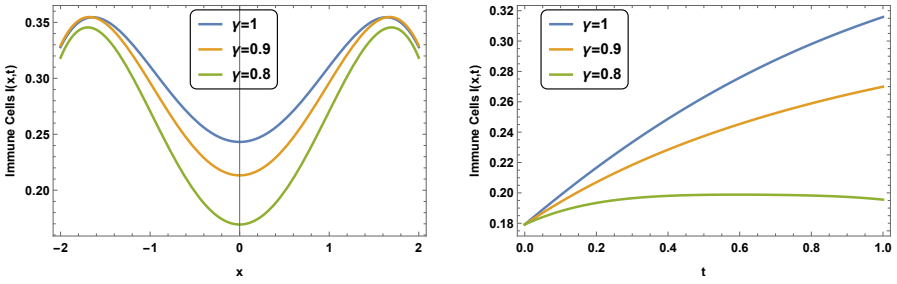
(a) along x-direction (b) along t-direction

FIGURE 5.3: Plots of normal cells $N(x,t)$ for different values of α



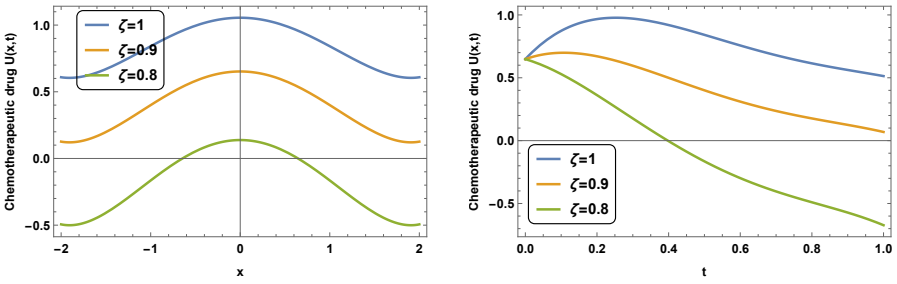
(a) along x-direction (b) along t-direction

FIGURE 5.4: Plots of tumor cells $T(x,t)$ at different values of β



(a) along x-direction (b) along t-direction

FIGURE 5.5: Plots of Immune cells $I(x,t)$ for different values of γ .



(a) along x-direction (b) along t-direction

FIGURE 5.6: Plots of concentration of chemotherapeutic drug $U(x,t)$ for different values ζ.

5.6 Conclusion

In this chapter, an approximation formula is developed for the C-F derivative of function $f(\xi) = \xi^{\sigma}$. By using this approximation, the C-F operational matrix of shifted Chebyshev polynomials is derived. The Chebychev collocation method is used to find the numerical solutions of FPDEs. The newly derived operational matrix is successfully implemented to find the solutions of C-F time fractional system of FPDEs having four coupled equations. The validity and accuracy of the considered method can be found from Table 5.2. From Fig.5.1 – 5.2, the conclusion can be drawn that growth of tumor cells has become less with time after the start of the chemotherapy treatment. This result is consistent with medical observation. In Figs.5.3 – 5.6, the effects of different fractional order parameters of the model on

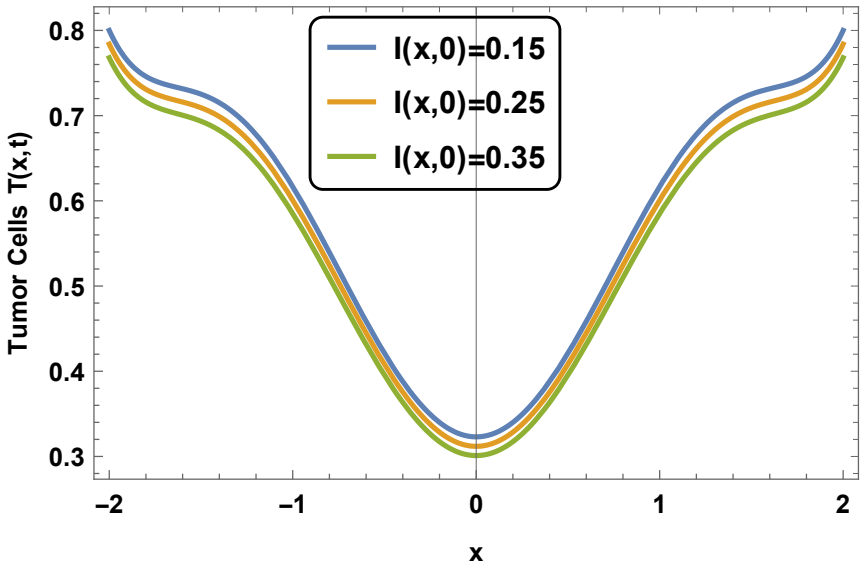


FIGURE 5.7: Dynamics of tumor cells at time $t = 0.5$ with different immune levels.

the normal, tumor and immune cells are studied. The figures depict the dynamics of different model parameters which include different fractional order parameters. The growth of tumor cells is more at invasive fronts $x = -1$ and $x = 1$ of tumor site in comparison with the center $x = 0$. Fig.5.7 shows that growth of immune cells increases with time. Considering the different types of immune levels towards the study of the effect of immune cells on the tumor cells, it can be predicted that a patient with a strong immune system will fight better against the growth of tumor cells.

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Chapter Template